(c) deprotecting the 5'-hydroxyl of the nucleoside with a deprotecting reagent comprising DCA in toluene;

(d) reacting the deprotected 5'-hydroxyl with an 5'-protected activated phosphorus compound to produce a covalent linkage therebetween;

(e) oxidizing or sulfurizing the covalent linkage to form a phosphodiester, phosphorothioate, phosphorodithioate or H-phosphonate linkage;

(f) repeating steps c through e at least once for subsequent couplings of additional activated phosphorus compounds, to produce the completed phosphorus-linked oligomer; and

(g) cleaving the oligomer from the solid support;

wherein steps (b) through (f) are performed using an automated device;

wherein said oligomer is a linear oligomer.

D3 concl'd

REMARKS

Claims 1-41 are pending in the present application. Claims 1 and 21 have been amended to recite that the oligomer be a linear oligomer. Support for the amendment can be found throughout the specification, and in the Examples, wherein linear oligomers are prepared. New claim 42 has been added which recites deprotection with DCA in toluene. Support for the new claim can be found in the specification at, for example, in Example 1 of the specification. No new matter has been added.

As a preliminary matter, Applicants bring to the Examiner's attention Horn, T., and Ureda, M.S., *Nucleic Acids Research* 17(17) 6959-6967 (1989) ("Horn et

al."), a copy of which is provided herewith for the Examiner's convenience.[1] The Horn et al. reference describes the synthesis of branched oligodeoxyribonucleotides. The Horn et al. reference states that the standard deprotecting reagent was found to be ineffective for deprotection of the synthesized branched DNA, and that trityl deprotection of such branched structures was achieved using 3% DCA in toluene. Applicants wish to note that in the context of the present invention, i.e., synthesis of linear oligonucleotides, the occurrence of branched structures such as described in the Horn et al. are contaminants to be avoided, and, in the event that such branch structures are produced, it is highly desirable to avoid deprotecting them, both to eliminate participation in further synthesis cycles, and in order to utilize the trityl groups to eliminate the contaminant from the final purified linear oligonucleotide. Thus, Applicants assert that those of skill in the art would not be led to use the stringent deprotection regime disclosed in Horn et al. for standard synthesis of linear oligonucleotides.

Claims 1-41 remain rejected under 35 U.S.C.§103(a) as allegedly obvious over U.S. Patent No. 5,705,621 to Ravikumar ("Ravikumar") in view of U.S. Patent No. 4,973,679 to Caruthers et al. ("Caruthers") and further in view of U.S. Patent No. 5,548,076 to Froehler et al. ("Froehler") and further in view of Sproat et al. (PTO-892 Ref.W), Conway, et al. (PTO-892 Ref.Y), Atkinson et al. (PTO-892 Ref.Z), and Sproat et al. (PTO-892 Ref. RA). Applicants respectfully request reconsideration and withdrawal of the rejection.

The Office Action has maintained its assertion that the cited art (in particular the Caruthers 679 and Froehler 076 patents) "motivate[s] the selection of practically any solvent mixtures which will dissolve the reactants and not otherwise interfere with the intended synthetic transformation." The Office Action further states

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[1] Applicants will shortly submit an Information Disclosure Statement and accompanying form PTO-1449 listing the Horn et al. reference under separate cover.

that the Ravikumar 621, Caruthers 679 and Froehler 076 references, and the "additional Caruthers et al. patents cited by Ravikumar et al. 621" describe:

> conventional prior art processes for making oligonucleotides via phosphoramidite or H-phosphonate intermediates, including the 5'-O-deprotection process step and including details of how the process has been automated in [Froehler et al.] and the patents cited in [Ravikumar 621].

Office Action at p. 6. The Office Action states that the cited portions of the Froehler 076 and Caruthers 679 patents teach that "the choice of a particular solvent or solvent mixture is a variable clearly within the purview of the ordinary practitioner." Id. The Office Action then states that the secondary references (the two cited Sproat et al. references, Conway et al. and Atkinson et al.) provide:

> ... disclosures that at least two different nucleoside 3'-O-phosphoramidites, at least one dinucleotide derivative, and some other nucleoside derivatives may be effectively dissolved in the aromatic hydrocarbon solvents benzene and/or toluene.

Office Action at page 7. The Office Action then posits that the disclosure of the solubility of such 3'-O-phosphoramidites, dinucleotide derivative, and "other" nucleoside derivatives provides:

> ... factually specific motivations for the ordinary practitioner conducting routine experimentation to substitute benzene, toluene, or their closely related aromatic solvent relatives as substitutes for at least a portion of the solvents typically used during the deprotection step in oligonucleotide synthesis."

Id. Thus, The Office Action appears to assert that the present claims are obvious because the primary references disclose that any solvent that can work is suitable, and the secondary references teach that certain nucleosides and derivatives are soluble in some

specific organic solvents. However, as discussed further below, Applicants disagree that the disclosure of solubility of the nucleosidic species recited by the Office Action motivate the use of Applicants' claimed deprotection solvents.

The Office Action on page 8 characterizes Applicants' statements regarding the use of the well-established oligonucleotide synthetic protocols as an "asserted reality wherein ordinary practitioners apparently avoid even thinking about optimizing the process via routine experimentation", and that the Examiner remains skeptical of "this view of automated oligonucleotide synthesis in light of the ongoing pressure of corporate business managers to minimize production costs, regardless of the production process."

Applicants first take issue with the Examiner's characterization of Applicants argument. Applicants do not assert, as the Office Action implies, that ordinary practitioners "avoid even thinking about" optimizing process conditions. What Applicants have asserted, and continue to assert, is that oligonucleotide synthesis is a well established field with standard protocols that are universally employed, and that because those of ordinary skill in the art are aware that the specific process conditions utilized in standard oligonucleotide synthesis (which are the result of years of research and volumes of publications detailing the kind of optimization described by the Examiner) require specific conditions of time, temperature, reagent and solvent at each deprotection and coupling step to ensure the optimal yield to provide a product suitable for intended uses such as, for example, research or pharmaceutical applications, there is no motivation to the art skilled to change those conditions to achieve Applicants' claimed invention.

The Office Action further characterizes Applicants' assertions of the criticality of following the established protocols as a "parade of horrors" that is a "straw man". Applicants strongly disagree with the Examiner's assertion, and view such comments as inappropriate.

The Office Action further states that:

> Applicant then argues at page 5, line 6 et seq [sic] that "[t]here is nothing in the art cited by the Office Action that would suggest the desirability of modifying the customary deprotection protocols use din [sic] automated oligonucleotide synthesis." Examiner notes that the rejection of record is under 35 U.S.C. §103(a) (obviousness), not 35 U.S.C. §102(b) (anticipation), and that applicant argument [sic] appears to be incorrectly assuming the latter rather than the former standard.

Office Action at page 9. Applicants respectfully disagree with the Examiner. Applicants assert that the present obviousness rejection is inappropriate because 1) as the Office Action admits, there is no teaching in the cited art of Applicants' claimed deprotection protocols; and 2) there is no motivation in the cited art or in the general skill in the art to modify the teaching of the cited art (i.e., customary oligonucleotide synthesis protocols) to achieve Applicants' claimed invention. As such, Applicants arguments regarding a lack of motivation to modify the cited art are clearly addressed to the obviousness rejection of record.

With regard to Applicants' assertion of lack of motivation described above, the Office Action states on page 9 that the cited art contains "repeated statements to the effect that the ordinary practitioner is free to select any solvent that works", and that "such routine experimentation is deemed to be within the scope of the cited art."

Thus, while the Office Action admits that none of the cited references teach Applicants' claimed deprotection solvent systems, the Office Action appears to assert that Applicants' claims are obvious because the primary references teach the use of "any solvent that works", and that the specific deprotection solvents claimed by Applicants are achievable by routine experimentation, which the Office Action deems to be within the scope of the cited prior art specifically because of the statements in that art

which "either fail to specify a required solvent or indicate that any solvent works as a substitute for the solvents used in the examples." Office Action at page 9.

Applicants again assert that the basis for the present rejection is improper. The Office Action admits that there is no teaching in the cited art of Applicants' claimed deprotection protocols. Indeed, the Office Action appears to admit that the prior art leads those of skill in the art to try **any** solvent "that works". However, this is not what is required for a determination of obviousness under the patent laws. Rather, what is required is a teaching motivating the use of the **claimed** deprotection solvents, and, as the Office Action appears to admit, there is no such teaching whatsoever in the cited art.

The Office Action asserts that motivation to use Applicants' claimed solvents is found in the broad disclosure of the prior art, and the suggestion therein that choice of solvent is not critical, which the Office Action deems "a clear suggestion and teaching that the scope of the prior art includes solvents not specifically referred to therein". Office Action at page 10. However, a suggestion that one try "any solvent that works" for a chemical transformation does not point those of skill in the art to those solvents that **will work**, but is rather merely an invitation to experiment. Thus, the present rejection appears to be based solely on an "obvious to try" rationale, which is clearly impermissible. See, e.g. *In re O'Farrell*, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). As such, the rejection is improper.

Because the Office Action fails to point to any motivation in the art to select Applicants' claimed deprotection solvents, Applicants respectfully request withdrawal of the rejection.

Applicants believe that the claims are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned

"VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully Submitted,

Date: October 3, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 1 and 21 have been amended as follows.

1. (Twice Amended) A method for the preparation of a linear phosphorus-linked oligomer comprising the steps of:

(a) providing a solid support;

(b) attaching a 5'-O-protected nucleoside to the solid support;

(c) deprotecting the 5'-hydroxyl of the nucleoside with a deprotecting reagent comprising a protic acid in a solvent to deprotect the 5'-hydroxyl of the nucleoside, the solvent being an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a halogenated alkyl aromatic solvent, or an aromatic ether solvent;

(d) reacting the deprotected 5'-hydroxyl with an 5'-protected activated phosphorus compound to produce a covalent linkage therebetween;

(e) oxidizing or sulfurizing the covalent linkage to form a phosphodiester, phosphorothioate, phosphorodithioate or H-phosphonate linkage;

(f) repeating steps c through e at least once for subsequent couplings of additional activated phosphorus compounds, to produce the completed phosphorus-linked oligomer; and

(g) cleaving the oligomer from the solid support;

wherein steps (b) through (f) are performed using an automated device;

wherein said oligomer is a linear oligomer.

21. (Amended) A method for the preparation of a linear phosphorus-linked oligomer comprising the steps of:

(a) providing a solid support;

(b) attaching a 5'-O-protected nucleoside to the solid support;

(c) contacting the protected 5'-hydroxyl of the nucleoside with a deprotecting reagent comprising a protic acid in a solvent to deprotect the 5'-hydroxyl of the nucleoside, the solvent being an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a halogenated alkyl aromatic solvent, or an aromatic ether solvent;

(d) reacting the deprotected 5'-hydroxyl with a 5'-protected activated phosphite compound to produce a phosphite linkage;

(e) oxidizing or sulfurizing the phosphite linkage to form a phosphodiester, phosphorothioate, or phosphorodithioate linkage;

(f) repeating steps c through e at least once for subsequent couplings of additional activated phosphite compounds, to produce the completed phosphorus-linked oligomer; and

(g) cleaving the oligomer from the solid support;

wherein steps (b) through (f) are performed using an automated device;

wherein said oligomer is a linear oligomer.

New claim 42 has been added.